REMARKS

Status of the Subject Application and the Present Response

Claims 1-3, 5-13 and 15-44 are pending in the patent application, with claims 21-44 being withdrawn as directed to non-elected inventions. Claims 1-3, 5-13 and 15-20 are under examination and stand rejected in the instant office action.

In the instant response, Claims 1 and 11 are amended to make it abundantly clear that the administered probe is specific for the reactive oxygen species. Support for the amendment is provided throughout the specification, e.g., inherently present in the disclosure at page 24, lines 1-8. In addition, claims 3 and 13 are amended to replace the recitation of "stilbene, or cholesterol" with "Amplex™ Red." This amendment has support in the specification, e.g., at page 30, lines 15-18

It is noted that the amendment is made to im make it abundantly clear that the administered probe is specific for the reactive oxygen species. prove clarity of the claim language, and that no new matter has been introduced. Applicants present the following remarks and arguments to address the issues raised by the Examiner in the office action.

Objection to the specification

Objection to the specification is maintained on the ground that singlet oxygen belongs to the broader genus of reactive oxygen species, and that the reference in the specification to conversion of "singlet oxygen" into "reactive oxygen species" is therefore repugnant to the art-recognized definition of reactive oxygen species. Applicants reiterate their willingness to address this objection once an allowable subject matter in the subject patent application is indicated by the Examiner.

New matter rejection under 35 U.S.C. § 112, 1st paragraph

Claims 1-3, 5-13 and 15-20 are rejected as allegedly failing to comply with the written description requirement. The Examiner asserts that the requirement in claims 1 and 11 for detecting probes that are oxidized in vivo by in vivo antibody-generated reactive oxygen species constitutes new matter. Applicants respectfully traverse this rejection.

First, to clarify, the pending claims only specify administering to a mammal a chemical probe for a reactive oxygen species, obtaining a sample from the mammal, and then detecting an oxidized product of the probe in the sample obtained. Contrary to the Examiner's assertion, the claims do not expressly recite probes that are "oxidized by in vivo antibody-generated" reactive oxygen species.

In addition, independent claims 1 and 11 as originally filed recite (1) administering to the mammal a chemical probe for reactive oxygen species; (2) obtaining a sample from the mammal; and (3) analyzing the sample for an oxidation product of the chemical probe. These claim elements, which are substantially reflected in the presently pending claims, clearly provides support for detecting an oxidized product of the probe in a sample obtained from the mammal which has been administered with the probe. Therefore, Applicants cannot see any new matter that is present in the currently pending claims.

If the alleged new matter rejection is actually based on the Examiner's belief that the invention as claimed may not work, then the issue should be raised under an enablement rejection. If the Examiner chooses to maintain this rejection, Applicants respectfully requests clarifications from the Examiner.

Enablement rejections under 35 U.S.C. § 112, 1st Paragraph

Claims 1-3, 5-13 and 15-20 were rejected as allegedly not enabled. The basis of the rejection, as asserted in the office action, appears to be that the specification only enables detection of probes that are in vitro oxidized by reactive oxygen species generated by antibodies in vitro, and that the specification does not enable detection of probes that are in vivo oxidized by reactive oxygen species generated by antibodies in vivo. In rendering the instant rejection, the Examiner also cited two references, Hewitt et al. (Ann. Rheum. Dis. 46:866-74, 1987) and Aaku et al. (Biochim. Biophys. Acta 1052:243-7, 1990), as evidence that the presently claimed invention is not enabled. Applicants respectfully traverse the rejection for the reasons stated below.

First, it is acknowledged that the subject specification may not have experimentally exemplified detection of a chemical probe that is oxidized in vivo by in vivo produced reactive oxygen species. However, it does not follow that the presently claimed invention is not enabled. As noted in the MPEP (§ 2164.02), the enablement requirement "does not turn on whether an example is disclosed," and "the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." With regard to correlation between in vitro and in vivo models, the MPEP notes that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." In the present case, there is no scientific basis or actual evidence to suggest that antibody cannot catalyze production of reactive oxygen species in vivo or that a chemical

probe for a reactive oxygen species cannot be oxidized by the reactive oxygen species in vivo. As explained in detail below, the references cited by the Examiner do not indicate otherwise.

The prior art, including the references cited by the Examiner, does not support the Examiner's assertion that antibody-catalyzed production of reactive oxygen species cannot be detected in vivo in accordance with the subject disclosure. Hewitt et al. reported that, upon inducing inflammation with UV-irradiated IgG in the air pouch model of inflammation in rats, effects of free radicals were analyzed by examining lipid peroxidation and damage to reisolated IgG in biological samples obtained from the rats. Results from some of the experiments indicate that there is no significant difference between test animals receiving free radical altered IgG and control animals receiving normal IgG. However, the lack of significant differences in some of the measurements in the two groups of animals does not stand for the proposition that antibodies cannot catalyze formation of reactive oxygen species in vivo to create detectable level of oxidized probes. This is because the normal IgG administered to the control animals are also able to produce reactive oxygen species in vivo. Such is consistent with the disclosure in Hewitt et al. that IgG reisolated from control animals also showed a progressive increase in the formation of damaged IgG (page 872, right column, second full paragraph). Thus, the data of Hewitt et al., if at all relevant to the present invention, may suggest that activities of free radicals in vivo as a results of administration of normal IgG and UV-irradiated IgG may be similar under certain experimental conditions. They do not suggest that there are no detectable free radical activities in the animals.

As to Aaku et al., this reference discussed the effect of

monomeric human IgG on neutrophil production of superoxide mediated by a specific chemotactic peptide fMLP. Aaku et al. noted that priming with IgG leads to enhancement of superoxide production by human neutrophils. It was shown in Aaku et al. that control cells not treated with the IgG were also able to release superoxide (Fig. 2). However, this does not prove that antibodies are not required for production of superoxide by the neutrophils. This is because, as disclosed in the subject specification, neutrophils are known to have antibodies on their cell surface (see, e.g., page 87, lines 9-12; and page 78, line 26 to page 79, line 3). This is the essence and underlying reason for ozone production by activated neutrophils as disclosed in the subject specification. Consistently, in the studies undertaken by the present inventors, no additional antibodies were supplied to the isolated neutrophils for production of ozone (see, e.g., pages 87-88). Thus, the IgG added to the neutrophils in Aaku et al. may merely stimulate neutrophil degranulation and enhance superoxide release, but is not itself essential to the observed superoxide production/release by the neutrophils. However, Aaku et al. does not negate antibody catalyzed production of reactive oxygen species that were discovered by the present inventors. Nor does the reference suggest that antibodies cannot similar function in vivo.

In addition, Aaku et al. also does not support the Examiner's conclusion that "prior art attempt to attribute reactive oxygen generation to antibodies are/were not successful due to background neutrophil-generated reactive oxygen." As explained above, because of the antibodies already present on neutrophils, antibody-catalyzed production of reactive oxygen species is not dependent on the added IgG in Aaku et al. To this end, it is noted the present claims do not require the addition

or administration of a further antibody in order to detect a immunological response or an inflammatory response. Applicants further note that the cited references actually provide support that the presently claimed invention would be scientifically accurate and technically feasible. This is because, an immunological response or an inflammatory response usually involves the activation of lymphocytes, neutrophils and/or other leukocytes (see the specification, e.g., at pages 26-28). Activation of these cells is usually associated with presence, production, and/or secretion of antibodies. Therefore, as disclosed in the subject specification and also evidenced in Aaku et al, antibodies produced by or present on the activated cells (e.g., activated neutrophils) will lead to production of reactive oxygen species. Therefore, one can reasonably expect that an administered chemical probe would react with a cognate reactive oxygen species and generate an oxidized product that can be readily detected in a biological sample isolated from the administered mammal, e.g., a serum sample as demonstrated in Hewitt et al.

From the above clarifications, it is clear that the present invention is enabled by the subject specification and knowledge well known in the art. Withdrawn of the instant rejection is accordingly requested.

Rejection under 35 U.S.C. § 102

Claims 1, 2, 5, 7-12. 15 and 17-20 were rejected as allegedly anticipated by Hewitt et al. Citing only the Abstract of Hewitt et al., the Examiner asserted that the reference described methods for detecting immunological or inflammatory responses by "administering a probe to the mammal," "obtaining a sample from the mammal" and "detecting an oxidized probe in the

sample." Applicants respectfully traverse this rejection for the reasons set forth below.

The claimed invention requires the administration of a probe for an antibody generated reactive oxygen species, and then detecting in a sample an oxidized product of the administered probe. By its plain meaning, a "probe" needs to be specific for the intended target so that the identity of the target can be revealed based on its reactivity with the probe. This feature of the subject invention is further clarified by the presently introduced amendments. Thus, the probe used in the present invention is specific for a target reactive oxygen species because the oxidized product of the probe should be indicative of the identity of the reactive oxygen species that catalyzes the oxidation. For example, Amplex® Red is a specific probe for hydrogen peroxide (see the specification, at page 30, lines 13-25). Similarly, oxidization of indigo carmine by ozone can be revealed by observing ^{18}O incorporation into the oxidized product via mass spectrometry (see the specification, at page 85, lines 8-24).

In contrast, Hewitt et al. does not teach or suggest a method as presently claimed. Instead, the IgG molecule administered to rats in Hewitt et al. is not a probe specific for any given reactive oxygen species. Rather, the modified IgG molecule (aggregates) as assessed in Hewitt et al. can be produced with any of a number of free radical generating systems (see, e.g., Lunec et al., J. Clin. Invest. 76:2084-90, 1985). In other words, detection of the modified IgG is not indicative of the presence of a specific reactive oxygen species.

In addition, if the UV-irradiated IgG administered to rats in Hewitt et al. is considered a "probe", Hewitt et al. does not teach or suggest detecting an oxidized product of this probe.

Instead, Hewitt et al. only discusses analyses of the probe itself (i.e., the damaged IgG molecule; see, page 867, section under "histochemistry and immunohistochemistry) or other molecules that are oxidized as a result of the induced inflammation in the rats (see, page 867, section under "Biochemical tests of free radical activity).

Applicants wish to reiterate that, to constitute anticipation, the claimed subject matter must be identically disclosed in a single prior art reference. *In re Arkley*, 172 USPQ 524 at 526 (CCPA 1972). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. V. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ 2d 101 (Fed. Cir. 1991). To overcome an anticipation rejection, "it is only necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172 (9th Cir. 1981). Applying the law of anticipation to the present case as clarified above, it is readily apparent that Hewitt et al. does not and could not anticipate the presently claimed invention. Withdrawal of the instant rejection is therefore respectfully requested.

Double patenting

Claims 1 and 11 are provisionally rejected as allegedly being unpatentable over claims 1, 5, 6, 11, 15 and 16 of co-pending Application No. 10/534,574 on the ground of obviousness-type double patenting.

In response, Applicants note that the instant rejection will be addressed once the allegedly conflicting claims in the co-pending claims are issued.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, please telephone the undersigned attorney at 858-784-2937. If there are any additional fees (or overpayments) associated with this Response, or any Response associated with this application, the Director is hereby authorized to charge (or credit) our Deposit Account No. 19-0962.

Respectfully submitted,

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Date

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